# Oral administration of caffeine metabolite 7-methylxanthine is associated with slowed myopia progression in Danish children

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**Abstract**

**Purpose:** Myopia is associated with an increased risk of permanent vision loss. The caffeine metabolite 7-methylxanthine (7-MX), licensed in Denmark since 2009 as a treatment to reduce the rate of childhood myopia progression, is the only orally-administered therapy available. The purpose of the current study was to assess the rate of myopia progression in children taking 7-MX.

**Methods:** Longitudinal cycloplegic refraction and axial length data for 711 myopic children from Denmark treated with varying doses of oral 7-MX (0-1200 mg per day) were analysed using linear mixed models.

**Results:** The median age at baseline was 11.1 years (range 7.0 to 15.0 years). Children were followed for an average of 3.6 years (range 0.9 to 9.1 years) and the average myopia progression was 1.34 Diopters (D) (range -6.50 to +0.75 D). Treatment with 7-MX was associated with a reduced rate of myopia progression ($p<0.001$) and axial elongation ($p<0.002$). Modelling suggested that, on average, an 11-year-old child taking 1000 mg 7-MX daily would develop -1.43 D of myopia over the next 6 years, compared to -2.27 D if untreated. Axial length in this child would increase by 0.84 mm over 6 years when taking a daily dose of 1000 mg of 7-MX, compared to 1.01 mm if untreated. No adverse effects of 7-MX therapy were reported.

**Conclusions:** Oral intake of 7-MX was associated with reduced myopia progression and reduced axial elongation in this sample of myopic children from Denmark. Randomised controlled trials are needed to determine whether the association is causal.

**Key messages.**

- **What is already known on this topic**

Oral 7-methylxanthine (7-MX) for myopia control was introduced in Denmark in 2009, but prior to the present study it has only been the subject of a pilot clinical trial. To evaluate the long-term effect of the treatment, data from myopic children receiving various doses of 7-MX were analysed using linear mixed models.

- **What this study adds**

An association between dose of 7-MX and 6-year modeled myopia progression and axial elongation was found.

- **How this study might affect research, practice or policy**

Existing myopia control intervention methods are not fully effective in preventing children from progressing to high myopia, and 7-MX may become a valuable supplement if causality and efficacy can be confirmed in future randomised controlled trials.

## Introduction

The excessive stretching and thinning of the retina, retinal pigment epithelium, and choroid associated with myopia may lead to complications including retinal detachment, myopic macular degeneration, and glaucoma. [1-2] Myopia often starts at the age of 6-7 years and progresses until the age of 16-20 years.[3] Currently available pharmacological and optical intervention methods do not completely arrest myopia progression.[4-8]

The caffeine metabolite 7-MX inhibits excessive axial elongation in two widely-used experimental models of myopia ("form deprivation myopia" and "lens-induced myopia") in guinea pigs, rabbits, and rhesus monkeys, [9-11] though not in form deprivation experiments in chickens, a species differing from mammals by having a sclera partly composed of cartilage.[12] Topically applied caffeine has also been reported to prevent experimentally-induced myopia, although the effect may be partly due to systemically absorbed caffeine.[13] Myopia is associated with a reduced concentration of scleral collagen; 7-MX has been reported to increase scleral collagen content, the diameter of collagen fibrils, and the thickness of the posterior sclera,[9-10, 14] potentially rendering the sclera more resistant to irreversible deformation. A pilot clinical trial, in which 7-MX was given in a dose of 400 mg once-per-day, showed a small but significant reduction of two-year axial elongation in myopic children aged 8-13 years, without any apparent adverse effects.[15] During the first year, in which the trial was placebo-controlled, myopia progression and axial elongation in 42 children randomised to placebo was -0.60 D and 0.30 mm compared with -0.52 D and 0.26 mm in 35 children randomised to 7-MX.[15] Due to its fast elimination (estimated half-life 3.3 hours), once-per-day dosing of 7-MX is probably sub-optimal. The Danish Medicines Agency (DMA) in 2009 authorised 7-MX for myopia control in children.

Caffeine (1,3,7-trimethylxanthine) has the status of "Generally Regarded as Safe" (GRAS) in the U.S.A. It can therefore be added to dietary products and sold over the counter without restrictions. Theobromine (3,7-dimethylxanthine), a first-order metabolite of caffeine, was

previously used to treat asthma in children in doses of up to 3000 mg per day. The acute and chronic toxicity of 7-methylxanthine (7-MX), a metabolite of theobromine, is several times lower than that of both caffeine and theobromine.[16-17] No morphological organ changes were found in rats given 1000 mg/kg body weight/day for 6 months, a dose equivalent to around 30,000 mg per day for a 7-year-old child.[17] In contrast to caffeine, 7-MX has poor ability to penetrate the blood-brain barrier.

The purpose of the current study was to assess the rate of myopia progression in children taking 7-MX.

## Methods

### *Study design*

This was a retrospective study of all longitudinal data collected from myopic children seen at one ophthalmology unit in Denmark over the period June 2000 to January 2021, excluding data from children using other myopia control methods than 7-MX. For 635 of the total sample of 711 children, measurement of cycloplegic refraction and axial length was undertaken as part of routine clinical ophthalmologist care. The remaining 76 children were participants in the aforementioned pilot trial.[15] Of the 711 children, 624 took oral 7-MX tablets and 87 children did not take 7-MX, either because they opted not to take part in the 2004 clinical trial, because they dropped out of same trial after taking placebo tablets for a year, or because they opted not to take 7-MX after the treatment had been authorized by the DMA in 2009. All myopic children seen at the ophthalmology unit starting June 2000 were encouraged to return for measurements at intervals not exceeding one year, regardless of whether they took part in the 2004 clinical trial or were only seen as part of routine clinical ophthalmologist care. Of the total sample of 711 children, 131 completed less than 700 days of follow up. However, 11 of these could not have had a longer follow up because their age at the next visit would have exceeded the upper age limit of 17 years. Another 23 children did not have a longer follow up because their last visit was less than one year before the data collection cut-off of January 2021. The

remaining 97 children could potentially have had a longer follow up but decided to discontinue. In most cases no reason was given. When a reason was given, it was most often that the child had not managed to take the tablets regularly, and the parents therefore saw no reason to continue follow up. In two cases the parents discontinued because they had expected higher efficacy of the treatment and in a few cases the child had moved to another part of the country. The DMA permits the use of 7-MX for treatment of myopia in children, hence ethical approval for this study was not required (the pilot trial was approved in October 2003 by the DMA and the Ethics Committee; www.clinical trials.gov - Reg.NCT00263471). Ethical approval for the analysis of clinical data to evaluate the effects of 7-MX was obtained from Cardiff University (reference: SREC-OPTOM-1571). Participants who completed all three years of the pilot trial had the option of continuing treatment with 7-MX. The routine clinical care of all 711 children included cycloplegic autorefraction and axial length measurement, as detailed below. Included in the current study were all children with an age-at-baseline between 7.0-15.0 years-old, a refractive error-at-baseline of at least -0.50 D and no use of other myopia control treatments. The follow-up period varied between children, from a minimum of 11 months to a maximum of 9 years (see Results section). 7-MX tablets (400 mg) were produced by Glostrup Apotek, Denmark using 7-MX supplied by Bioplus Life Sciences (Bangalore, India). Initially, children were prescribed one tablet daily (morning), but from 2011 prescription was changed to 2 tablets daily (800 mg in total, one tablet morning and evening), and from 2017 it was changed to 3 tablets daily (1200 mg in total, one tablet approximately every 8 hours). At each visit, the number of tablets supplied to the child was obtained from a central register and parents were asked how many tablets remained. The daily dose of 7-MX was calculated as 400 mg × number of tablets taken, divided by the number of days since the last visit.

***Ophthalmic measurements***

Ocular refraction was measured using a Retinomax autorefractor (Nikon, Japan) 30 minutes after a single drop of 1% cyclopentolate. Spherical equivalent was calculated as the sphere

power plus half of the cylinder. Axial length was measured with an IOL-Master (Carl Zeiss Jena GmbH, Germany). Four consecutive IOL-Master readings were averaged. The same autorefractor and IOL-Master were used throughout the study. The avMSE was defined as the spherical equivalent refractive error averaged between the 2 eyes. The avAXL was defined as the axial length averaged between the 2 eyes.

***Data analysis***

To account for the longitudinal nature of the study and the non-uniform interval between visits, data were analyzed using linear mixed models. This approach allowed all children to be included irrespective of their length of follow-up. Linear mixed models have been used previously to examine myopia progression longitudinally.[18-22] avMSE and avAXL were assigned as the primary and secondary outcome. Sensitivity analyses were performed in which each eye was analyzed separately. The precise interval between visits to the clinic was modelled as a random effect nested within subjects, assuming an autoregressive correlation structure. We were unable to model the exact dose of 7-MX received throughout each part of the study, therefore the average daily dose of 7-MX each child received over the total duration of the study was calculated, i.e. the cumulative dose of 7-MX divided by the time the child was in the study. Gender (male/female), age-at-baseline (years), and average daily dose of 7-MX were included as fixed effects. Refractive error-at-baseline (D) or axial length-at-baseline (mm) were accounted for in the model when avMSE or avAXL was the outcome variable, respectively. To account for potential non-linearity in the relationship between the outcome and children's age, higher-order terms for the interval between visits were included. We also tested for interactions between the fixed effect variables. The goodness of fit of models was assessed by comparing minus 2 × the log likelihood (using a likelihood ratio test for nested models that had different degrees of freedom). It was assumed that the relationship between average daily 7-MX dose and the rate of myopia progression was linear. Simple linear regression was used to explore factors associated with the total number of visits that children attended. Analyses were performed using the R

statistics package *nlme*.[23] The anonymised clinical data and code for replicating the analyses are included in the Supplementary Material.

## Results

### *Demographic characteristics of the sample*

Data were available for 711 children, 356 girls and 355 boys (Table 1). The mean age at baseline was 10.9 years (median 11.1; range 7.0 to 15.0 years) and the mean refractive error at baseline was -2.43 D (median -1.94; range -9.00 to -0.50 D). The children spent an average of 3.6 years in the study (median 3.3; range 0.9 to 9.1 years). Attendance at the clinic usually occurred annually. The total number of visits varied from 2 to 10, with 70% (n=500) of children completing at least 4 visits and 31% (n=217) completing at least 6 visits. Annual myopia progression during the period that children remained in the study was -0.38 D/year (median -0.35; range -1.78 to +0.50 D/year). Mean axial length at baseline was 24.4 mm (median 24.4; range 22.2 to 28.1 mm) and the mean annual axial elongation over the course of the study was 0.21 mm/year (median 0.20; range -0.08 to 0.87 mm/year). The average daily dose of 7-MX was 470 mg/day (median 530; range 0 to 1120 mg/day). A total of 87 (12.2%) children did not receive 7-MX.

### *Modelling of refractive error and axial length trajectory*

Longitudinally assessed refractive error was modelled assuming that children in the study were drawn randomly from a large sample with a characteristic pattern of refractive development. Individual differences from this underlying pattern were assumed to be normally distributed around the mean. The model allowed for treatment efficacy to vary non-linearly over time, to take account of the potential for treatment efficacy in the early years of treatment to be higher than in later years. The relationship between daily 7-MX dose and treatment efficacy was assumed to be linear.

Parameter estimates for the fixed effect terms in the best-fitting models for the outcomes avMSE and avAXL are presented in Table 2. Figure 1 provides examples of the avMSE model fits for 25 individual children. It is evident from Figure 1 that fitting the model to the data from all 711 children constrained the path of the fitted refractive error trajectory, such that more extreme observations that did not follow the general pattern were down-weighted. For example, for "Child B" in Figure 1, observations 5 and 6 were down-weighted relative to the other observations. The inclusion of terms for age-at-baseline and gender did not improve the model fit for avMSE but these terms did improve the model fit for avAXL ($p < 0.001$ for both). Therefore, for consistency, these terms were retained in both models.

When terms for both a "7-MX dose" main effect and a "7-MX dose × time-from-baseline" interaction were included in the model, there was strong evidence to support the presence of the interaction ($p < 0.001$) but not the "7-MX dose" main effect ($p = 0.13$). This was also true when a "7-MX dose × time-from-baseline^2" term was included, to account for a potential decline in treatment efficacy over several years of 7-MX use. As shown in Supplementary Table S1, omission of the "7-MX dose" main effect had little influence on the parameter estimates for the other terms in the model. Therefore, to simplify the interpretation of the model, the "7-MX dose" main effect was dropped from the final models (Table 2). In clinical terms, omission of the main effect term for 7-MX dose is equivalent to assuming that there was no difference in the baseline refractive error of children who would later receive a relatively high or low dose of 7-MX. Note that omission of a main effects term, yet including it in an interaction, does not invalidate a regression model, although it does alter the interpretation of the parameter estimates.[24]

Figure 2 illustrates 6-year-duration refractive error and axial length trajectories predicted by the best-fitting models. These predicted trajectories can be considered as representative of those for a "typical" myopic child presenting at a specified age-at-baseline and receiving a

specified daily dose of 7-MX over the next 6 years. The analysis suggested that for a typical child presenting at age 7 years-old with a baseline refractive error of -2.53 D, without treatment the child's myopia would increase by -3.49 D over the next 6 years. The analysis suggested a daily dose of 1000 mg of 7-MX was associated with a reduced rate of progression, such that the same child's myopia would increase by -2.65 D over 6 years. In terms of axial elongation, the analysis suggested that without treatment, axial length would increase by 1.80 mm over 6 years, whereas it would increase by 1.63 mm over 6 years when taking a daily dose of 1000 mg of 7-MX. For a typical child presenting at age 11 years-old with a baseline refractive error of -2.49 D, without treatment the child's myopia would increase by a further -2.27 D over the next 6 years. With a daily dose of 1000 mg of 7-MX, the analysis suggested the child's myopia would increase by -1.43 D over 6 years. In terms of axial elongation, the analysis suggested that without treatment, axial length in this child would increase by 1.01 mm over 6 years, whereas it would increase by 0.84 mm over 6 years when taking a daily dose of 1000 mg of 7-MX.

Clinical trials of myopia treatments sometime set inclusion criteria imposing limits on the baseline refraction. To evaluate whether restricting the baseline myopia level had an impact on the effect associated with 7-MX treatment, models were fitted after excluding children whose levels of myopia at baseline exceeded a threshold of -8.00, -6.00, -4.00 or -2.00 D. As shown in Supplementary Figure S1, excluding children with progressively more stringent thresholds led to models with shallower refractive error trajectories, such that, on average, children had lower levels of myopia at the completion of the study. However, the reduced rate of myopia progression associated with 7-MX treatment was similar irrespective of the stringency of the baseline myopia threshold. For example, for a child first seen at age 9 years and followed until age 15 years, taking 1000 mg/day 7-MX was associated with a 26-34% reduction in the final degree of myopia, compared to not taking 7-MX across the spectrum of threshold (-8.00 to -2.00 D; Supplementary Figure S1).

Forty-eight study children did not exhibit myopia progression during the study (ΔavMSE = +0.20 D on average; Supplementary Figure S2). As shown in Supplementary Table S2, the group who did not experience myopia progression had an older age-at-baseline (median 12.4 vs. 11.0 years, $p < 0.001$), stayed in the study for a shorter duration (median 2.5 vs. 3.5 years, $p < 0.001$) and received a higher daily dose of 7-MX (median 670 vs. 500 mg/day, $p < 0.001$). The 2 groups did not differ in their baseline level of refractive error ($p = 0.13$).

***Factors associated with number of clinic visits (duration in the study)***

If children who experienced a high rate of myopia progression decided to drop out of the study at an early stage, this could bias the analysis – potentially causing the estimated "treatment efficacy" associated with 7-MX to be over-estimated. Therefore, factors associated with the number of clinic visits were investigated. As an index of the rate of myopia progression during the early stages of the study, a new variable "progression-at-3$^{rd}$-visit" was derived by calculating the myopia progression per year between the 3$^{rd}$ and baseline visits (this typically covered a 2-year interval). The results are shown in Table S6 and Figure 3. There was a little evidence that children with faster progression-at-3$^{rd}$-visit attended fewer visits ($p = 0.54$; Figure 3A) or that boys were more or less likely to stay in the study than girls ($p = 0.24$; Figure 3B). Children who joined the study at an older age were more likely to drop out than children who joined at an earlier age (each year increase in age-at-baseline was associated with attending approximately 0.4 fewer visits on average, $p < 0.001$; Figure 3C). This association presumably reflected the decision of individuals in the sample to leave the study once they reached late teen-age. Refractive error-at-baseline was associated with the number of clinic visits children attended; however, the effect was small (a baseline refractive error that was lower than average by -1.00 D was associated with attending 0.1 fewer clinic visits; Table S6).

***Choice of outcome variable***

Analyses in which the outcome variable was the refractive error in just the right eye or just the left eye yielded similar parameter estimates as the model for avMSE (Table S3 and Table S4).

Parameter estimates were also similar for a model in which the refractive errors of both right and left eyes were nested within subjects (Supplementary Table S5) but note that it was not possible to specify an autoregressive correlation structure when fitting this more complex, nested model. These findings suggested that using avMSE as the primary outcome variable did not have a major impact on the results compared to other possible choices of the outcome variable.

***Adverse effects***

For participants taking part in the 2004-2008 pilot trial[15], height, weight, blood pressure and heart rate were measured, and the participants were interviewed systematically about possible subjective adverse effects. As reported previously[15], no differences between placebo- and 7-MX-treated children were observed. For children undergoing routine clinical ophthalmological care, parents were asked to report adverse effects. Since this is a study of a treatment previously allowed by the DMA, a screening protocol for side-effects was not required. Denmark has a well-functioning system for reporting side-effects of pharmacological treatment. No potential side-effects relating to 7-MX have been reported to the DMA since the treatment was introduced in 2009.

## Discussion

In this observational study, the dose of 7-MX that children received was associated with their rate of myopia progression. Importantly, the study design only allowed us to conclude that an increased dose of 7-MX was *associated* with slowed myopia progression and axial elongation. However, the *causality* of the treatment is supported by experimental studies in animal models. The question of causality and the size of a possible treatment effect can only be determined through a randomised trial.

The analysis suggested that without treatment, an 11-year-old child with a baseline refractive error of -2.49 D would have a progression of -2.27 D over the next 6 years. In a previous study of

Danish children with a mean age of 11 and a mean refraction of -2.77 D at baseline,[25-26] the refractive error 8 years later was -5.14 D, corresponding to a progression of -2.37 D. Since myopia progression after the age of 17 is generally relatively slow, the value predicted by the model seems to be in accordance with this earlier study. The same study found a two-year myopia progression of -1.14 D and axial elongation of 0.5 mm, but axial length was not measured 8 years after the initial visit.

A relatively small number of children received thrice-per-day dosing. This may have affected the accuracy of the estimates for children taking more than 800 mg per day. In addition, since complying with taking 3 tablets per day is more demanding than taking 2 tablets per day, it is possible that the children who took a high dose on average had parents that were more motivated, for example because the myopia was progressing at an above-average rate. Such biases are unavoidable in studies based on observational datasets of treated patients.

Since causality has not been established, we cannot make definite statements about the efficacy of 7-MX. However, an earlier one-year trial showed 0.04 mm less axial elongation in children taking 400 mg once per day compared with placebo[15] and given the inverse relationship between axial elongation and 7-MX dose, higher doses of 7-MX are presumably more effective. Our model predicts around 0.07 mm less axial elongation during the first year for children taking 1000 mg per day compared with children not taking 7-MX and an accumulated reduction of 0.18 mm over 6 years. A treatment effect of this magnitude would be clinically meaningful as it lowers the risk of myopia related complications. For comparison, low-concentration atropine eye drops (<0.1 %) reduce eye elongation by around 0.1 mm during the first year of treatment.[27]

There were four children (one age 10 years and three age 12 years) with +0.5 D or more of "myopia regression" during the time they remained in the study (range 364 to 1633 days). In all four cases, the myopia regression was accompanied by negative axial elongation (range -0.225

to -0.015 mm), and they were all children who took 7-MX (range 398 to 757 mg per day). In three of the cases, the axial length reduction exceeded what can be explained by choroidal thickening, suggesting that contraction of the sclera had occurred.

Because of the fast elimination of 7-MX from the bloodstream, the presently available immediate release tablet is not capable of maintaining a stable concentration in the bloodstream, even when given three times per day. A sustained release formulation of 7-MX given once or twice per day is theoretically a more effective way to administer the treatment.

At the concentrations applied in the current study, the main effect of 7-MX is to block adenosine receptors (ADORs). There are four ADOR subtypes, ADORA1, ADORA2a, ADORA2b, and ADOR3, all present in all layers of the posterior segment of the eye.[28-30] ADORA2b is only activated by high concentrations of adenosine as produced by tissue damage, hypoxia, or inflammation.[31] Since 7-MX has limited ability to penetrate the blood-brain barrier[32] and presumably little ability to penetrate the blood-retina barrier, other structures than the retina, such as the sclera, the choroid, or the retinal pigment epithelium are likely targets for 7-MX. Thinning of the choroid, a phenomenon hypothesized to function as a "go" signal for axial elongation, is prevented by 7-MX in rhesus monkeys fitted with minus lenses.[11] 7-MX seems to enhance hyperopia in rhesus monkeys fitted with plus lenses,[11] a finding suggesting that 7-MX potentially could boost the efficacy of optical devices designed to reduce myopia progression. 7-MX stimulates collagen type I and fibronectin production in cultivated human scleral fibroblasts but inhibits their production in choroidal fibroblasts.[33] Methylxanthines have anti-inflammatory effects in a variety of tissues.[34] Retinal inflammation and scleral hypoxia, conditions associated with increased levels of adenosine and up-regulation of ADORA2b,[35] may be involved in the pathogenesis of myopia.[36-37]

**Limitations**

The current study had important limitations compared to the gold-standard approach of a randomised controlled trial. The length of follow-up varied widely, there was no randomly-selected control group and, being an observational study, there may have been links between the dose of 7-MX taken by the child and factors known to affect myopia progression such as age, severity of myopia, myopia in parents, time spent outdoor, time spent on near work, or ethnicity (for example, parents who were themselves myopic may have had a greater incentive for their child to receive the highest available dose of 7-MX). Accordingly, causality could not be established. In addition, due to ethnic and environmental differences, the findings may not apply to populations outside Denmark.

## Ethics statement

The Danish Ethics Committee has defined the study as quality control of a previously authorised new treatment and the study is therefore exempted from ethical approval.

Ethical approval for the analysis of clinical data to evaluate the effects of 7-MX was obtained from Cardiff University (reference: SREC-OPTOM-1571).

**Authorship confirmation statement:** All authors participated in planning of the study, statistical analysis or writing of the manuscript.

**Competing interests statement:** Klaus Trier, none. Dongmei Cui, none. Søren Munk Ribel-Madsen, none. Jeremy A. Guggenheim, none.

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**Table 1. Demographic characteristics of the study sample.** Values are median (25$^{th}$ percentile to 75$^{th}$ percentile). P-values are for a Mann-Whitney test of the null hypothesis of no difference in the median value between boys and girls. avMSE and avAXL refer to the spherical equivalent refractive error and axial length averaged between fellow eyes, respectively.

| Variable | All | Female | Male | p-value |
|---|---|---|---|---|
| Sample size | 711 | 356 | 355 | |
| Age at baseline (years) | 11.07 (9.46 to 12.49) | 11.20 (9.38 to 12.46) | 10.88 (9.49 to 12.51) | 0.720 |
| avMSE at baseline (D) | -1.94 (-3.25 to -1.12) | -2.06 (-3.19 to -1.12) | -1.88 (-3.31 to -1.12) | 0.580 |
| avAXL at baseline (mm) | 24.42 (23.79 to 24.96) | 24.10 (23.54 to 24.77) | 24.64 (24.09 to 25.21) | $1.20 \times 10^{-13}$ |
| Annual myopia progression (D/year) | -0.35 (-0.53 to -0.19) | -0.40 (-0.57 to -0.22) | -0.32 (-0.50 to -0.15) | $2.40 \times 10^{-4}$ |
| Annual axial elongation (mm/year) | 0.20 (0.12 to 0.27) | 0.20 (0.13 to 0.28) | 0.19 (0.11 to 0.26) | 0.050 |
| Cumulative myopia progression (D) | -1.06 (-1.88 to -0.50) | -1.19 (-1.95 to -0.62) | -1.00 (-1.81 to -0.41) | 0.006 |
| Cumulative axial elongation (mm) | 0.59 (0.34 to 0.99) | 0.60 (0.36 to 1.00) | 0.59 (0.31 to 0.98) | 0.230 |
| Average daily dose 7-MX (g) | 0.53 (0.23 to 0.68) | 0.50 (0.22 to 0.66) | 0.54 (0.24 to 0.69) | 0.190 |

**Table 2. Parameter estimates for best-fit linear mixed model for the outcomes "avMSE" and "avAXL".** All n=711 children were included in the analysis.

| | Refractive error (avMSE) | | | Axial length (avAXL) | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Coefficient** | **SE** | **p-value** | **Coefficient** | **SE** | **p-value** |
| Intercept | -4.57 | 0.40 | $8.04 \times 10^{-30}$ | 24.52 | 0.20 | $<1.00 \times 10^{-100}$ |
| Gender (male) | -0.12 | 0.13 | 0.355 | 0.51 | 0.07 | $1.78 \times 10^{-14}$ |
| Age-at-baseline (years) | 0.01 | 0.03 | 0.729 | 0.08 | 0.02 | $3.01 \times 10^{-6}$ |
| Time-from-baseline (years) | -103.21 | 6.20 | $3.38 \times 10^{-59}$ | 58.77 | 2.37 | $<1.00 \times 10^{-100}$ |
| Time-from-baseline$^2$ (years$^2$) | 10.69 | 1.10 | $4.36 \times 10^{-22}$ | -5.87 | 0.37 | $5.54 \times 10^{-55}$ |
| Time-from-baseline$^3$ (years$^3$) | 0.96 | 0.35 | 0.006 | 0.27 | 0.11 | 0.016 |
| Age-at-baseline (years) × Time-from-baseline (years) | 0.05 | <0.01 | $4.03 \times 10^{-25}$ | -0.03 | <0.01 | $8.91 \times 10^{-68}$ |
| 7MX-dose (g/day) × Time-from-baseline (years) | 0.30 | 0.04 | $2.50 \times 10^{-12}$ | -0.08 | 0.02 | $3.24 \times 10^{-7}$ |
| 7MX-dose (g/day) × Time-from-baseline$^2$ (years$^2$) | -0.03 | 0.01 | 0.001 | 0.01 | <0.01 | 0.002 |

**Figure 1. Refractive error trajectory model fits for a subset of 25 children.** The refractive error (avMSE) at each visit is plotted as open circle symbols. Refractive error trajectory model fits are indicated by the blue curves.

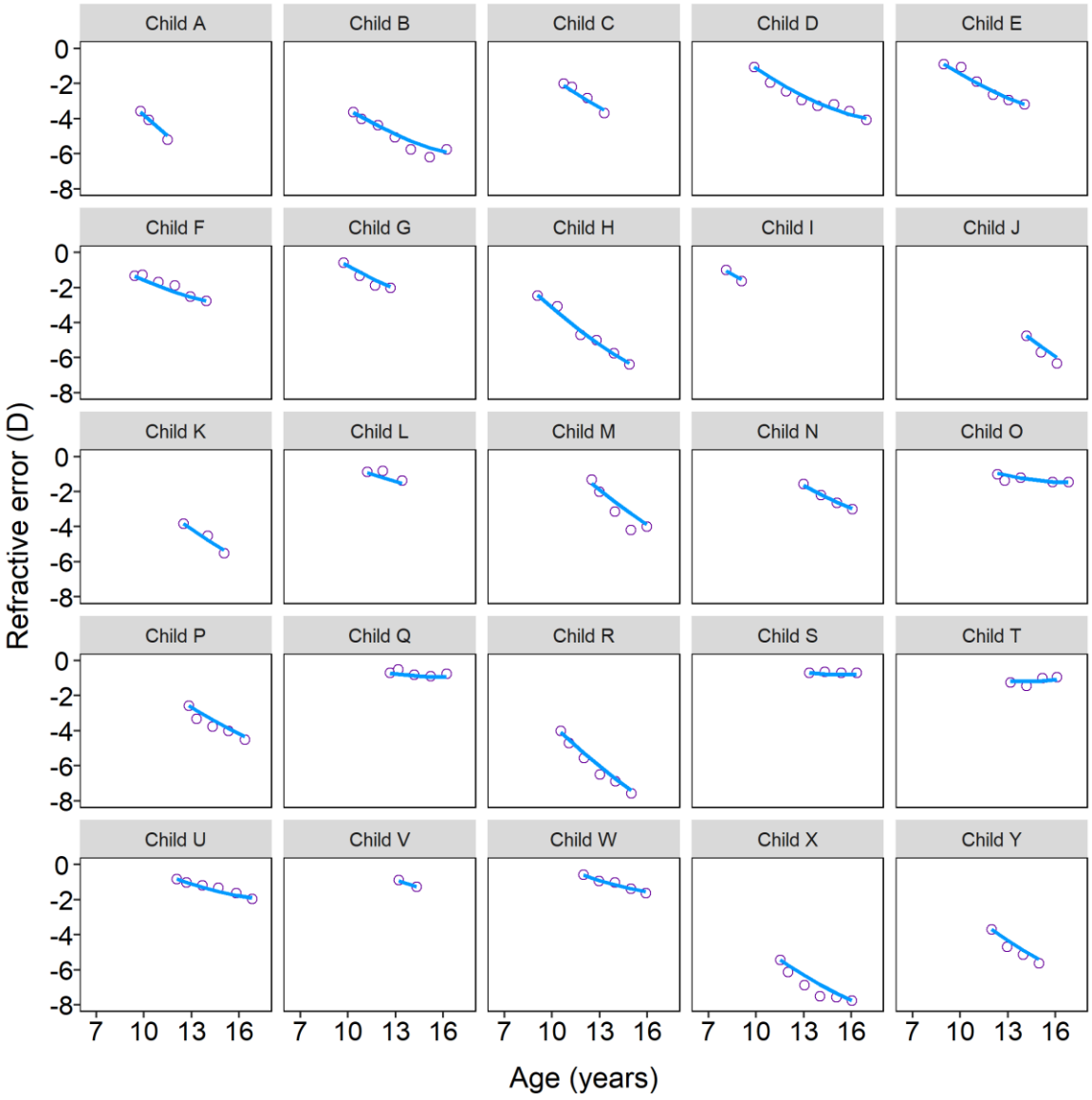

**Figure 2. Refractive error trajectory models for the full sample of 711 children.** The refractive error (**A**) and axial length (**B**) trajectories predicted by the best-fitting model for children based on their baseline age and the average daily dose of 7-MX, assuming a linear relationship between 7-MX dose and treatment efficacy.

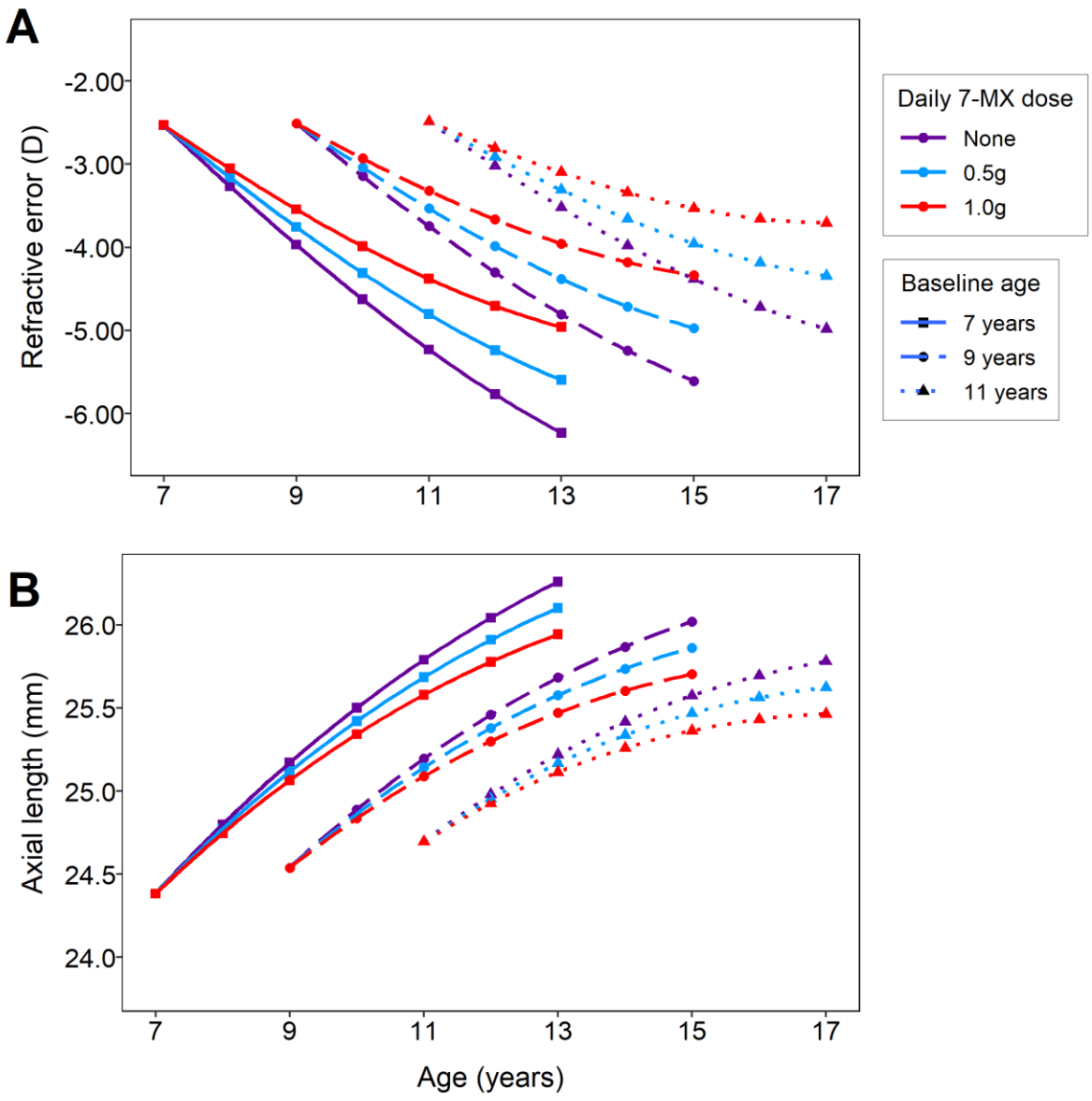

**Figure 3. Factors associated with remaining in the study.** Data are for children who attended at least 3 clinic visits (n=645).